CHRONIC TOXICITY SUMMARY

ETHYLENE OXIDE

(oxirane, dimethylene oxide, epoxyethane)

CAS Registry Number: 75-21-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**30** µ**g/m^3** (18 ppb)
Critical effect(s)	Neurotoxicity in rats
Hazard index target(s)	Nervous system

II. Physical and Chemical Properties (HSDB, 1995; CRC, 1994)

Description	Colorless gas
Molecular formula	C_2H_4O
Molecular weight	44.06 g/mol
Density	1.80 g/L @ 25ºC
Boiling point	10.6ºC
Melting point	–111.6ºC
Vapor pressure	1095 torr @ 20ºC
Conversion factor	1 ppm = 1.80 mg/m^3

III. Major Uses or Sources

The majority of all ethylene oxide (EtO) produced is used as a chemical intermediate in the production of various compounds including ethylene glycol, glycol ethers, and non-ionic surfactants (ATSDR, 1990). EtO is also used as a fumigant for food and cosmetics, and in hospital sterilization of surgical equipment and heat sensitive materials such as plastics. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 43,972 pounds of ethylene oxide (CARB, 2000).

IV. Effects of Human Exposure

Ten hospital sterilizer workers were matched with controls and examined for physical and neuropsychological health (Estrin *et al.*, 1990). The workers had operated sterilizers using 12% EtO and 88% Freon for an average of 5 years (range 0.5-10 years). Regular monitoring of workroom air had not been done. Measurements at the time of the study indicated concentrations of 15 ppm EtO or less. However, a second measurement showed an air concentration of 250 ppm EtO. A significantly greater percent of exposed workers exhibited

a bilateral reflex reduction in the ankle compared to controls. Nerve conduction tests did not identify significant differences between control and exposed workers, but a highly significant reduction ($p = 0.009$) in finger tapping speed was observed in exposed workers. The exposed group also performed more poorly on tests of spatial and visual abilities, and on tests of visual motor function. The results extended previous work by the same group (Estrin *et al*., 1987).

Cognitive impairment and personality dysfunction were observed more frequently in hospital workers chronically exposed to EtO, compared to a control group (Klees *et al.*, 1990). A group of 22 hospital workers, who had been exposed to an 8-hour TWA of 4.7 ppm EtO for a mean of 6.13 years (range 1-11 years), were matched with 24 control subjects. Neuropsychological function in the workers was classified as either normal or impaired on the basis of the questionnaires and of neuropsychological tests by 2 clinical psychologists (who were unaware of exposure status). (If the classification of the two clinicians did not agree, the subject was classified as "disagreement." Disagreement occurred in 7/23 (30%) of the controls and 10/22 (45%) of the exposed.) Exposed subjects were significantly more frequently classified as impaired (5/12) compared to controls (1/16) ($\chi^2 = 6.0861$; $p<0.05$). The Klees *et al*. (1990) study cites several earlier case reports of EtO neurotoxicity.

Recent studies have identified hemoglobin adducts, sister chromatid exchanges, and other hematological effects as indicators of ethylene oxide exposure (Ribeiro *et al.*, 1994; Sarto *et al.*, 1991). However, a recent study of 68 female workers from 9 hospitals in the U.S. and one in Mexico not only reports biological indicators of ethylene oxide exposure, but also provides a complete blood count with differential (Schulte *et al.*, 1995). The workers were classified as low- or high-exposure based on a mean 8-hour time weighted average of 0.08 or 0.17 ppm EtO. The mean length of employment for workers from U.S. hospitals was 5.5 and 10 years for low- and high-exposure workers, respectively. The mean length of employment in low- and high-exposure workers from the hospital in Mexico was 5.9 and 4.2 years, respectively. In workers from U.S. hospitals only, statistically significant decreases in hematocrit and hemoglobin were observed in high-exposure workers compared to low-exposure workers. Also, a statistically significant increase in lymphocytes and a significant decrease in neutrophils were observed in high-exposure workers compared to controls. In the workers from the hospital in Mexico, a significant relationship of EtO exposure and elevated neutrophil count was observed using regression.

At least 2 epidemiological reports indicate a possible association of EtO exposure and spontaneous abortion. Hemminki *et al.* (1982) analyzed spontaneous abortions in Finnish hospital sterilizing staff using data from a postal questionnaire and from a hospital discharge register. The study included all sterilizing staff employed in Finnish hospitals in 1980; the controls were nursing auxiliaries. When the women were involved in sterilizing procedures during their pregnancies, the frequency of spontaneous abortion was 16.7% versus 5.6% for the non-exposed pregnancies. The independent analysis of spontaneous abortions using the hospital discharge register confirmed the findings. Thus two analyses suggested that EtO exposure may carry a risk of spontaneous abortion among sterilizing staff.

More recently Rowland *et al*. (1996) sent questionnaires to 7,000 dental assistants (ages 18-39 years) registered in California in 1987. Of these, 4,856 responded (69%). They analyzed

1,320 women whose most recent pregnancy was conceived while working full-time. Thirty-two reported exposure to EtO; unexposed dental assistants comprised the comparison group. Among exposed women, the age-adjusted relative risk (RR) of spontaneous abortion was 2.5 [95% (CI) = 1.0-6.3]. The RR for pre-term birth was 2.7 (95% CI = 0.8-8.8) and the RR for post-term birth was 2.1 (95% CI = 0.7-5.9). The RR of any of these adverse outcomes among exposed women was estimated to be 2.5 (95% CI = 1.0-6.1). These results also indicate a possible relationship of EtO and spontaneous abortion.

V. Effects of Animal Exposure

A 2 year inhalation bioassay exposed groups of 80 male rats to 0, 50, or 100 ppm EtO 7 hours per day, 5 days per week for 104 weeks (Lynch *et al.*, 1984). Mean body weights were significantly lower and mortality was significantly higher in both exposure groups. Inflammatory lesions of the lung, nasal cavity, trachea, and inner ear were observed more frequently in EtO exposed rats. Skeletal muscle myopathy, consisting of atrophy and degeneration of skeletal muscle fibers, was observed more frequently in rats exposed to 100 ppm EtO compared to controls. Neoplastic changes were also observed in EtO exposed rats.

Mice (30 per sex) were exposed to 0, 10, 50, 100, or 250 ppm EtO for 6 hours per day, 5 days per week, for 10 weeks (males) or 11 weeks (females) (Snellings *et al.*, 1984). Neuromuscular screening was conducted, and samples of urine and blood were collected. A significantly greater percent of exposed mice exhibited abnormal posture during gait and reduced locomotor activity. A dose-response was observed for these effects, with significant changes at 50 ppm and greater. An abnormal righting reflex was observed in a significantly greater percent of mice exposed to 100 ppm and above. Reduced or absent toe and tail pinch reflexes were observed in a significantly greater percent of mice exposed to 250 ppm EtO. Hematological changes observed in mice exposed to 250 ppm include slight, yet significant, decreases in red blood cell count, packed cell volume, and hemoglobin concentration. Absolute and relative spleen weights were significantly decreased in female mice exposed to 100 and 250 ppm and in male mice exposed to 250 ppm EtO. A significant increase in relative liver weight was observed in female mice exposed to 250 ppm EtO. Male mice exhibited a significant decrease in body weight at 10, 50, and 250 ppm and a significant decrease in absolute testes weights at 50, 100, or 250 ppm EtO. This study indicates a subchronic NOAEL for neurological effects of 10 ppm EtO.

In a study of the testicular effects of EtO, male rats were exposed to 500 ppm EtO 6 hours per day, 3 days per week for 2, 4, 6, or 13 weeks (Kaido *et al.*, 1992). An awkward gait was observed in rats after 6-9 weeks of exposure. Although no significant changes in body weight were observed, a statistically significant dose-related decrease in testes weight was observed at 4, 6, and 13 weeks of exposure. Progressive degeneration and loss of germ cells were also observed during the 13 week exposure. While severe loss of germ cells and marked morphological changes in remaining germ cells were observed at 6 weeks of exposure, some intact spermatids were observed at 13 weeks of exposure. This suggests that recovery of spermatogenesis occurred.

Saillenfait *et al*. (1996) studied the developmental toxicity of EtO in pregnant Sprague-Dawley rats using inhalation exposure during gestation days 6 to 15. Two protocols were used: (1) exposure for 0.5 hr once a day to 0, 400, 800, or 1200 ppm EtO; or (2) exposure for 0.5 hr three times a day to 0, 200, or 400 ppm EtO or to 0, 800, or 1200 ppm EtO. The second protocol caused fetal toxicity as indicated by reduced fetal weight at 800 ppm (the LOAEL for this endpoint) and at 1200 ppm, and overt maternal toxicity manifested as reduced body weight gain at 1200 ppm. No embryolethality or teratogenicity occurred in either exposure protocol.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Snellings *et al*., 1984
Study population	Male and female B6C3F1 mice
Exposure method	Inhalation chamber exposure to 0, 10, 50, 100, or 250 ppm ethylene oxide
Critical effects	Impaired neurological function
LOAEL	50 ppm
NOAEL	10 ppm
Exposure continuity	6-hours/day, 5 days/week
Exposure duration	10 weeks (males), or 11 weeks (females)
Average experimental exposure	1.79 ppm (10 x 8/24 x 5/7)
Human equivalent concentration	1.79 ppm ((gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h)))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	18 ppb (30 $\mu g/m^3$)

Snellings *et al*. (1984) found a subchronic NOAEL of 10 ppm for neurological effects in mice. A neuromuscular screening test indicated that certain reflex responses and locomotor activities were altered in EtO-exposed animals. Human studies have also indicated neurological impairment in ethylene oxide exposed workers.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for ethylene oxide include the use of an animal study with both a LOAEL and a NOAEL and the use of an endpoint seen in both animals and humans.

Major areas of uncertainty are the short time-frame of the key study, the lack of an appropriate human study, and the limited number of developmental toxicity studies.

VIII. References

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